Atom Economical Syntheses of Oxygen Heterocycles via Tandem Palladium-Catalyzed Reactions

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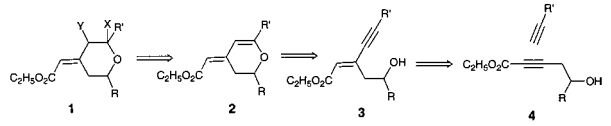
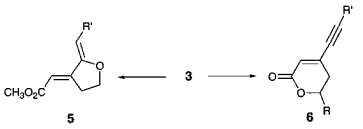
The control of alkene geometry exocyclic to a ring represents a formidable task. Recent work directed toward the synthesis of bryostatins and other natural products because of their promising antitumor activity demonstrates the problem of synthesizing a tetrahydropyran exemplified by **1**.[1] Accessing such compounds via the dihydropyran **2** suggested the prospect of a simple atom economic strategy based upon the 6-endo-dig[2] cyclization of **3** which could derive from the palladium-catalyzed addition of terminal alkynes onto ynoates **4**.[3,4] Two potential competing

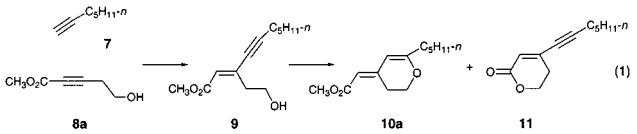


processes to the 6-endo-dig cyclization are immediately apparent—a 5-exo-dig cyclization to diene **5** or a simple lactonization to *δ*-pentanolactone **6**. While such competing processes appear



highly probable, the prospect of a one-step simple synthesis of dihydropyrans **2** led us to examine the feasibility of this strategy.[5]

To test the concept, the reaction of 1-heptyne (**7**) and methyl 5-hydroxy-2-pentynoate (**8**) (see eq 1) catalyzed by palladium acetate with tris-(2,6-dimethoxyphenyl)phosphine[6] as ligand was examined as summarized in Table 1. Following the reaction by thin-layer chromatography revealed that formation of the simple adduct **9** occurred completely within 24 h; but cyclization proceeded very slowly (entry 1). Allowing the reaction to proceed for a prolonged period of time gave the dihydropyran **10a** in satisfactory yield as the only detectable product. Increasing the



reaction temperature after adduct **9** formed to 50 °C (entry 2) or simply running the reaction at 50° (entry 3) led to a significant reduction in reaction time with about the same yield but gave rise to competitive formation of lactone **11**. Repeating these protocols but using 80 °C (entries 4 and 5) led to reduction in time for consumption of starting materials but significant losses in yield and selectivity. A workable solution was found by increasing the catalyst loading (entry 6) whereby a 61% isolated

Table 1. Effect of Reaction Conditions on Addition of Alkyne **7** and Alkynoate **8a**[a]

entry	mol % $Pd(Oac)_2$	mol % TDMPP	temp °C	time/ days	% isolated yield	ratio **10:11**
1	5	2	rt	5.5	61	>20:1
2	5	2	rt to 50°[b]	2.5	61	5.5:1
3	5	2	50°	2.25	57	5.5:1
4	5	2	rt to 80°[b]	1.5	30	1.8:1
5	5	2	80°	1.0	23	1.6:1
6	10	4	rt	2.5	61	>20:1

[a] All reactions performed in benzene at a concentration of 0.7 M in substrates **7** and **8a**. [b] Reaction run at rt for the first 24 h followed by heating to the stated temperature.

yield of dihydropyran **10a** was isolated as the only product. Using these conditions, a variety of hydroxyalkynoates in the reaction with 1-heptyne were examined as summarized in Table 2.[7] Converting the primary alcohol into a secondary (entries 2−5) and even tertiary (entry 6) one led to successful reaction albeit with some yield loss in the last case. Remarkably, the reaction tolerated a vicinal chlorohydrin (entry 5) with only a modest loss in yield. On the other hand, the *trans*-hydroxyalkynoate **12** gave the expected adduct **13** within 2 days (eq 2, 50% isolated yield). Use of more forcing conditions gave no dihydropyran but only lactone **14**, which was isolated in 58% overall yield from **12**.

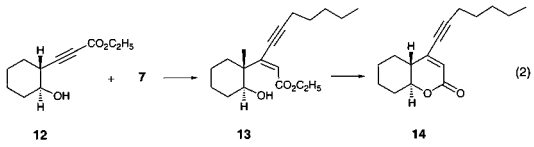
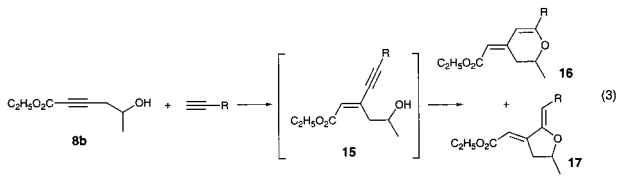


Table 3 and eq 3 summarize the effects of varying the terminal alkyne partner in the reactions with homopropargylic alcohol **8b**. While increasing the steric hindrance of R to cyclopentyl had no discernible effect (entry 1), switching to *tert*-butyl dramatically slowed the cyclization rate (entries 2 and 3). Envisioning that



the cyclization was also a palladium acetate-catalyzed reaction, its rate should depend on the electrophilicity of the palladium(+2) species wherein increasing electrophilicity should increase the cyclization. We have previously noted the dramatic enhancement of rate in formation of *π*-allylpalladium complexes from less nucleophilic alkenes upon using palladium trifluoroacetate.[8] In the initial experiment, the trifluoroacetate salt was generated in situ by simply adding trifluoroacetic acid to palladium acetate. Indeed, the cyclization rate increased dramatically (complete cyclization in 1 day), but a 1:1 mixture of the exocyclic alkene

(1) (a) Evans, D. A.; Carter, P. H.; Carriera, E. M.; Charette, A. B.; Prunet, J. A.; Lautens, M. *J. Am. Chem. Soc.* **1999**, *121*, 7540. (b) Baxter, J.; Mata, E. G.; Thomas, E. J. *Tetrahedron* **1998**, *54*, 14359. (c) Obitsu, T.; Ohmori, K.; Ogawa, Y.; Hosomi, H.; Obha, S.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1998**, *39*, 7349. For a review of earlier synthetic approaches to the bryostatins, see: Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041.

(2) (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. (b) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc., Chem. Commun.* **1976**, 736.

(3) Trost, B. M.; Sorum, M. T.; Chan, C.; Harms, A. E.; Ruhter, G. *J. Am. Chem. Soc.* **1997**, *119*, 698.

(4) Trost, B. M.; McIntosh, M. C.; *J. Am. Chem. Soc.* **1995**, *117*, 7255.

(5) For recent examples of dihydropyran synthesis, see: (a) Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635. (b) Cacchi, S.; Fabrizi, G.; Larock, R. C.; pace, P.; Reddy, V. *Synlett* **1998**, 888.

(6) Wada, M.; Higashizaki, S. *J. Chem. Soc., Chem Commun.* **1984**, 482.

(7) All new compounds gave satisfactory spectral and physical data.

(8) Trost, B. M.; Metzner, P. J. *J. Am. Chem. Soc.* **1980**, *102*, 3572.

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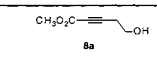
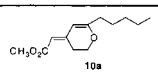
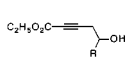
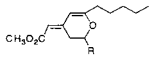
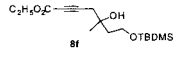
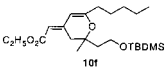
Table 2. Variation of Hydroxyalkynoate[a]

Entry	Hydroxy-alkynoate	Product	Time/days	% Isolated Yield
1	 **8a**	 **10a**	2.5	61
				
2	R = CH_3 **8b**	R = CH_3 **10b**	2.5	57
3	R = CH_2OPMB **8c**	R = CH_2OPMB **10c**	7.0	57
4	R = $CH_2OTBDMS$ **8d**	R = $CH_2OTBDMS$ **10d**	7.0	52
5	R = CH_2Cl **8e**	R = CH_2Cl **10e**	7.0	42
6	 **8f**	 **10f**	7.0	44

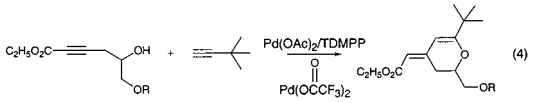
[a] All reactions performed using 10% mol $Pd(OAc)_2$ and 4% mol TDMPP and a 1:1 ratio homopropargylic alcohol/alkyne at a concentration of 0.7 M in benzene at rt (Procedure A).

Table 3. Variation of Terminal Alkyne[a]

Entry	Alkyne	Major Product	Time/ days	Ratio **16**:**17**	Isolated Yield(%)
1		**16a**, R = 	2.5	ONLY **16**	57
2	$-C_4H_9$-*t*	**15b**, R = *t*-C_4H_9	2.0	N.A.[c]	70
3	$-C_4H_9$-*t*	**16b**, R = *t*-C_4H_9	14.0	ONLY **16**	25
4[d]	$-C_4H_9$-*t*	**16b**, R = *t*-C_4H_9	3.5	ONLY **16**	62
5	$-C_6H_5$	**16e**, R = -C_6H_5	2.5	6.2:1	57
6	$-CH_2OH$	**16d**, R = CH_2OH	2.0	2.3:1	50
7	$-CH_2CH_2OH$	**16e**, R = CH_2CH_2OH	2.0	7.5:1	62
8	$-(CH_2)_4OH$	**16f**, R = $(CH_2)_4OH$	2.5	ONLY **16**	51
9	$-C(OH)(CH_3)_2$	**17g**, R = $C(OH)(CH_3)_2$	3.0	1:4.2	41
10	$-(CH_2)_3CN$	**16h**, R = $(CH_2)_3CN$	2.0	6.9:1	50

[a] All reactions performed using 10 mol % $Pd(OAc)_2$ and 4 mol % TDMPP in benzene at rt using 1:1 ratio of substrates at 0.7 M (Procedure A) unless stated otherwise. [b] Determined by ^1H NMR spectroscopy. [c] N.A. = not applicable. [d] Reaction performed in two stages: stage 1 using 4 mol % $Pd(OAc)_2$ and 4 mol % TDMPP and stage 2 using 6 mol % $Pd(OCOCF_3)_2$ (Procedure B).

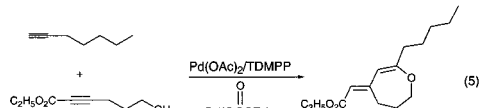
isomers of **16** (R = *t*-C_4H_9) was isolated in 59% yield.[9] When ancillary experiments revealed that isomerization of double bond geometry was catalyzed by Bronsted acids, the protocol was changed to utilize a 1:1 mixture of palladium acetate and TDMPP for the initial addition (stage one) followed by addition of palladium trifluoroacetate for the cyclization (stage two).[10] In this way, a rapid conversion of the two alkyne starting materials directly to the dihydropyran occurred in a one-pot reaction. The effectiveness of this protocol is highlighted by the success of the example of eq 4 wherein the dihydropyrans **18** are isolated in good yields—a type of substitution that bodes well for the more complicated substrates needed for natural products syntheses.



8d R=TBDMS
8c R=PMB

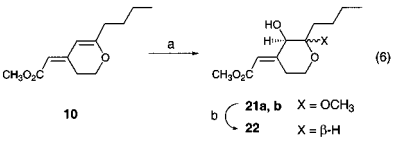
18a R=TBDMS (55% yield)
18b R=PMB (61% yield)

Placing a conjugating substitutent like phenyl on the terminal alkyne (entry 5) makes the 5-exo dig cyclization to **17c** (R = Ph) now compete with the 6-endo dig product (**16c**, R = Ph) although the latter was strongly preferred.[11] A propargylic alcohol substituent had a much stronger effect on this competition (entry 6), but this fell off dramatically as it was moved farther away from the triple bond (entries 7 and 8). A reasonable explanation of this substitutent effect on regioselectivity derives from the negative inductive effect of the electronegative hydroxyl group which disfavors generation of positive charge at the proximal alkyne carbon necessary for cyclization to dihydropyran. On the other hand, the combination of the inductive effect and the steric effect in entry 9 reverses the regioselectivity such that the 5-exo dig product now dominates. The inductive effect also accounts for the small deterioration of the regioselectivity in entry 10. The two-stage one-pot catalytic system employing the combination of palladium acetate and palladium trifluoroacetate allowed the extension to the formation of seven-membered rings (eq 5), a cyclization that completely fails in the absence of the palladium trifluoroacetate.



19 **20** (56% yield)

It is possible to achieve selective oxidation of the enol ether olefin of the dihydropyrans produced by this method (eq 6). Treatment of dihydropyran **10a** with *m*-CPBA in CH_2Cl_2/MeOH[12] gave a 2.5:1 mixture of isomers at the anomeric center. Treatment of this mixture with triethylsilane and boron trifluoride diethyl etherate at low temperature effected reduction of the anomeric center to give a single product assigned as *E*−**22** based upon coupling constants.



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(a) *m*-CPBA, CH_2Cl_2/MeOH (2:1), 79% (2.5:1 mixture of diastereomers.

(b) Et_3SiH, BF_3OEt_2, CH_2Cl_2, -78°C, 63% from **10a** (single diastereomer).

This one-pot alkyne/alkynoate coupling provides complex dihydropyrans in moderate to good yields and in a highly atom economical fashion. The reaction utilizes simple starting materials that, by themselves, are easily accessed taking advantage of alkyne chemistry. For example, the homopropargylic alcohols needed for the synthesis of dihydropyrans easily derive from the epoxide ring opening with the acetylide derived from ethyl propiolate. The reaction is also highly chemoselective tolerating esters, free alcohols, silyl ethers, PMB ethers, nitriles, and alkyl chlorides. The exocyclic double geometry is created with high control that is mechanism-based. Indeed, both steps are palladium(+2) catalyzed events. The dihydropyrans are promising intermediates for complex pyrans that are difficult to access by other synthetic means.

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Supporting Information Available: Experimental details (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) The structure of the isomerized exocyclic enoate (*E* geometry) was assigned on the basis of ^1H NMR data—the chemical shift of the vinyl ring proton was shifted downfield relative to the *Z*-enoate, while the ring protons allylic to the exocyclic enoate were shifted upfield relative to the *Z*-enoate.

(10) When palladium trifluoroacetate was used alone, cross-coupling of the alkyne and the ynoate was unsuccessful.

(11) Structure assignment was based on the observation of *J*-coupling between a vinyl proton and the protons adjacent to a hydroxyl group, consistent with the structure of the product of 5-exo dig cyclization rather than 6-endo dig cyclization.

(12) Wender, P. A.; De Brabander, J.; Harran, P. G.; Jimenez, J.-M.; Koehler, M. F. T.; Lippa, B.; Park, C.-M.; Shiozaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 4534.